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ABOUT TYPHUS AND PARATYPHUS IMMUNIZATIONS BY  
MEANS OF MIXED TYPHUS AND PARATYPHUS VACCINE  
AND THE RESULT OF IMMUNIZATION IN THE IMPERIAL  
JAPANESE NAVY

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To Wright belongs the credit for having accomplished the active immunization against typhus by means of destroying broths or ure first to a great extent in human beings. The results which Wright obtained by his extensive immunization in English Colonial Army were quite suitable. Pfeiffer and Kolle used as inoculum fresh agar-cultures which by heating to 60° were sterilized. This last method has obtained in practice quite suitable results as the different publications about the experience in German Southwest Africa demonstrate.

Still in recent times publications from different lands exist which report on the results of typhus immunization. Leishman obtained excellent results in the case of the English troop divisions dispatched to the tropics. With his inoculation, heated for 1 hour, he established that in the case of equal opportunity of infection the number of illnesses in the vaccinated amounted to 3.7% while the illness among the not vaccinated amounted to 32.8%. The knowledge concerning the immunization against paratyphus is quite a bit less, probably mainly because the clinical symptoms in the case of this disease occur milder than in the typhus and because the

mortality rate is scarcely less. Kolle, Kutscher, Meinicke and others have proved that the animals vaccinated with dead or live paratyphus bacteria are able to tolerate multiple lethal doses of paratyphus bacillus.

The statistics of the Imperial Japanese Navy show that typhus cases pointed out since 1902 have increased and in 1907 have reached their high point. In 1907 and '08 the sick rate amounted to 9.2% and 7.2% respectively in the whole crew. In 1909 the number of typus sick decreased quickly. Moreover, the basis is probably that on the one hand in this year paratyphus was separated from typhus and that on the other hand immunization was cut off, just as it is compared below.

Table I

Typhus cases in the Imperial Japanese Navy in the last five years (1907-1911).

	Typhus illness	Sick rate per 1000	Deaths	Mortality per 1000
1907	372	9.20	34	0.84
1908	307	7.00	32	0.73
1909	118	2.63	22	0.49
1910	212	4.78	28	0.63
1911	106	2.31	13	0.28

Table II

Paratyphus cases (typhus A) in the Imperial Japanese Navy in the last five years (1907-1911).

	Paratyphus illness	Sick rate per 1000	Deaths	Mortality per 1000
1907	0	0		
1908	143	3.12	1	0.02
1909	105	2.29	5	0.11
1910	101	2.20	1	0.02
1911	45	0.98	0	0

Table 3

Paratyphus cases (type B) in the Imperial Japanese Navy  
in the last five years (1907-1911).

	Paratyphus illness	Sick rate per 1000	Deaths	Mortality , per 1000
1907	18	0.45	0	
1908.	212	4.93	0	
1909	60	1.03	0	
1910	104	2.27	0	
1911	362	7.89	0	

An epidemic of typhus and paratyphus occurred on a ship. They appeared very stubborn against all prophylactic precautions such as disinfection, isolation and so on. In the case of epidemics there are often detected a number of bacillus carriers. That makes it necessary to carry out immunizations for the whole crew. The immunization was carried out according to the Pfeiffer and Kolle method. The number of vaccinations supplied for the years 1908 to 1911 was 28,343 against typhus, 18,834 against paratyphus A and 11,884 against paratyphus B. Those vaccinations against typhus show 63.6%, paratyphus A 42.0%, and paratyphus B only 27.3% of the whole crew. The fact that the sickness in regard to paratyphus and typhus have declined considerably since 1908 just as the above indicated table shows, one must connect it to the introduction of the immunization. The remarkable behavior is expressed in the mortality rate, namely:

Mortality per 1000		
Typhus	Vaccinated	2.4
	Not vaccinated	18.6
Paratyphus A	Vaccinated	3.8

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Mortality per 1000.

Paratyphus A	Not vaccinated	8.7
Paratyphus B	Vaccinated	0
	Not vaccinated	14.0

But the statistic is not wholly reliable because in the case of such large scales unavoidable mistakes occur. But the observations of the sick is quite reliable which were received and taken care of in 5 Navy hospitals (Yokosuka, Kure, Sasebo, Maisuru, and Riojun).

Table 4

Sick which were received in Navy Hospitals from 1909-1911.

		Typhus	Paratyphus A	Paratyphus B
Sick		367	289	447
Vaccinated	diseased	68	71	0
	dead	5	2	
Not	diseased	299	218	447
vaccinated	dead	40	5	0

As this table shows, the number of sick amounts to only  $\frac{1}{2}$  in those vaccinated against typhus and  $\frac{1}{2}$  in those vaccinated against paratyphus A in comparison to the number of sick who were not vaccinated. The mortality rate of the vaccinated is only half as large as those not vaccinated; in case of paratyphus A one finds in comparison no difference in the number between the vaccinated and not vaccinated.

According to our experience the duration furnished up to the eruption of illness (by vaccination) is as follows:

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	Typhus	Paratyphus A
within 3 weeks	5(7.35%)	39(54.93%)
3 weeks to 1 year	47(69.13%)	29(40.84%)
1 to 2 years	5(7.35%)	2(.2.82%)
2 to 3 years	9(13.24%)	0
over 3 years	2( 2.94%)	1(1.41%)
Total	68	71

The number of fatal cases from typhus sickness which were not vaccinated were compiled in the following cases.

Number of deaths of typhus sickness which have been vaccinated.

Duration of the inoculation up to sickness	Deaths	Amt. of vaccination bacillus	Reaction to vaccination
5 months	3	0.9 mg.	slight
17 months	1	0.7 "	"
3½ years	1	0.3 "	"
Total	5		

Number of deaths from paratyphus A sickness which have been vaccinated

Duration of the inoculation up to sickness	Deaths	Amt. of vaccination bacillus	Reaction to vaccination
2 months	1	0.7 mg.	slight
10 months	1	0.7 mg.	"
Total	2		

As the above mentioned tables show there are only three deaths under the typhus sickness and 2 under paratyphus within a year after immunization occurs. Therefore let it be noted that the amount of vaccine was very slight and insufficient.

In the Imperial Japanese Navy it occurs often that on one and the same ship typhus and paratyphus appear simultaneously. But when the immunization against typhus and paratyphus A or B is not able to protect opposites so it has been considered practical immunization against all three illnesses together.

In the case of immunization we are dealing with an active immunization, so more or less reactions to the inoculation will be eliminated. Recently Kolle, Hetsch, Kutscher and others have proved resistance of serum inoculation and have come to the conclusion "the more powerful the reaction the greater the resistance". In execution of inoculation it is therefore up to a known degree unavoidable that ship maneuvers, formation and exercise will injure the sailors. Therefore, the experiment was prepared this way to lighten the trouble and the immunization with the mixture of typhus and paratyphus was performed at once. Moreover the occasion simultaneously offered to prove the strength of reaction and of the formation of protective bodies was injured.

#### 1. Research on animals

The experiment was performed as follows: first of all I made vaccine by mixing equal amounts of 24 hour typhus and paratyphus A and B agar culture. This vaccine contains bacillus bodies in different quantities and 2.1, 0.4, 0.2 and 0.02 mg. in 1 ccm. of vaccine. Two series of guinea pigs

were used in this experiment, the first was inoculated once with the aforementioned vaccine but the other was inoculated twice. As control animals two series were used. On the 10th day after the last immunization all the animals were injected intraperitoneally with a 5 fold lethal dose of culture to prove the protective strength of the vaccine. The procedure is reproduced in the following tables:

Table 5

The mixed vaccine contains 1 ccm. 2mg., the simple 0.7 mg. bacillus in 1 ccm, thus 1/3 that of the mixed vaccine.

Weight of guinea pig g	Kind of vaccine	Innoca- lution	Infectious dose ( 5 fold lethal dose)	Results
	Mixed vaccine			lived
230	Typhus		Typhus	lived
230	+ Paratyphus	once	Paratyphus A	*
235			Paratyphus B	lived
200	A and B		Typhus	"
225		twice	Paratyphus A	"
290			Paratyphus B	"
Control (single vaccine)				
240	Typhus		Typhus	lived
235	Paratyphus A	once	Paratyphus A	*
230	" B		" B	lived
255	Typhus		Typhus	*
210	Paratyphus A	twice	Paratyphus A	lived
225	" B		" B	"

Table 6

The mixed vaccine contains 1 ccm. in 1mg. the single 0.3 mg. bacillus bodies in 1ccm, thus 1/3 of that of the mixed vaccine.

Weight of guinea pig	Kind of vaccine	Innoculation	Infectious dose (5 fold lethal dose)	Results
3				
310			Typhus	lived
300		once	Paratyphus A	*
325	Typhus +		" B	lived
310	Paratyphus			"
320	A and B	twice	Typhus	"
270			Paratyphus A	"
			" B	*
Control				
220	Typhus		Typhus	lived
240	Paratyphus A	once	Paratyphus A	*
240	" B		" B	lived
285	Typhus		Typhus	*
325	Paratyphus A	Twice	Paratyphus A	survived
250	" B		" B	"

Table 7

The mixed vaccine contains in 1 ccm 0.4 mg., the single 0.13 mg. bacillus thus 1/3 the amount of mixed vaccine.

Weight of guinea pig	Kind of vaccine	Innoculation	Infectious dose (5 fold lethal dose)	Results
5				
220			Typhus	*
310		once	Paratyphus A	lived
260	Typhus +		Paratyphus B	*
260	Paratyphus		Typhus	lived
310	A and B	twice	Paratyphus A	"
315			" B	*
Control				
340	Typhus		Typhus	*
310	Paratyphus A	once	Paratyphus A	lived
370	" B		" B	*
240	Typhus		Typhus	*
260	Paratyphus A	twice	Paratyphus A	lived
235	" B		" B	*

Table 8

The mixed vaccine contains in 1 ccm 0.2 mg., the single 0.07 mg. bacillus in 1 ccm. thus 1/3 of the amount of mixed vaccine.

Weight of guinea pig g	Kind of vaccine	Innoca- lution	Infectious dose ( 5 fold lethal dose)	Results
270			Typhus	lived
255			Paratyphus A	"
220	Typhus +	once	" B	*
205	Paratyphus		Typhus	lived
230	A and B	twice	Paratyphus A	*
220			" B	lived
Control				
210	Typhus		Typhus	lived
270	Paratyphus A	once	Paratyphus A	"
240	" B		" B	*
265	Typhus		Typhus	*
190	Paratyphus A	twice	Paratyphus A	lived
190	" B		" B	"

Table 9

The mixed vaccine contains in 1 cc. 0.1 mg., the single 0.03 mg. bacillus in 1ccm, thus 1/3 the amount of mixed vaccine.

Weight of guinea pig g	Kind of vaccine	Innoca- lution	Infectious dose ( 5 fold lethal dose)	Results
200			Typhus	lived
180			Paratyphus A	*
180	Typhus	once	" B	lived
190	Paratyphus		Typhus	"
190	A and B	twice	Paratyphus A	"
200			" B	"
Control				
175	Typhus		Typhus	*
215	Paratyphus A	once	Paratyphus A	lived
225	"		" B	"
245	Typhus		Typhus	"
190	Paratyphus A	twice	Paratyphus A	*
270	"		" B	lived

Table 10

The mixed vaccine contains in 1ccm 0.02 mg., the single in 0.007 mg. bacillus in 1ccm, thus 1/3 the amount in the mixed vaccine.

Weight of guinea pig g	Kind of vaccine	Innocu- lation	Infectious dose ( 5 fold lethal dose)	Results
230			Typhus	*
200		once	Paratyphus A	lived
200	Typhus		" B	*
250	Paratyphus		Typhus	lived
180	A and B	twice	Paratyphus A	*
220			" B	lived
<hr/>				
Control				
210	Typhus		Typhus	lived
186	Paratyphus A	once	Paratyphus A	lived
160	" B		" B	*
195	Typhus		Typhus	lived
200	Paratyphus A	twice	Paratyphus A	*
185	" B		" B	lived

As one notes in these tables there is no difference observed between the protective power of the single and the mixed vaccine.

## 2. Research on human bodies

Because in the case of immunization with the mixed vaccine a strong reaction was feared the vaccine was made in 2 concentrations, and indeed so much that one contained 1ccm per 2 mg. of bacillus and the other 3 mg. Twenty four hour typhus and paratyphus A and B were mixed in sterile physiological sodium chloride and filtered through sterile gauze. This suspension was sterilized through 2 hour shaking in a double bath at 60°C and then was mixed in 0.5% phenol. After the sterility had been accurately adjusted the inoculum was decanted.

With a vaccine produced so the head naval doctor, Dr. Kato had to carefully vaccinate the crew on the battleship "Yatori" and subject the same to careful and precise observation. With the expectation that the inoculum would produce a violent reaction he injected 3 per 1 ccm, instead of 1 per 3 ccm. The reaction was not especially violent. The dose amounted to at the beginning of the first inoculum 1 ccm in the second 2 ccm. But in order to avoid injection of such a large amount the concentration of the bacillus suspension was doubled. After the experience of the surgeon general Dr. A. Hirana, however, after which by Dr. Katzu and staff doctor Dr. Orimo the reactions to the concentrated inoculum were not much stronger than to the dilute. Therefore it is evident that the reactions do not occur parallel to the amount of bacteria.

The reactions to the inoculum with mixed vaccine were as follows: in the majority of the cases on the average 2 to 4 hours later there appears near the injection an intensive mostly sharp limited redness about the size of the palm of the hand and slow burning around the place of inoculation. Occasionally there was also a painful swelling in the region of the lymphatic glands. The reactions disappear almost completely after 48 hours.

In the following table the important reactions are compiled.

Table 11

Reactions to the inoculum with mixed vaccine in comparison to the inoculum with the single vaccine.

Inoculum	Frost feeling	Chills	Headache	Vertigo	Pain in joints	Loss of appetite	Vomiting	Diarrhea	Lymphangitis	Swelling of the Lymphatic glands
Mixed Vaccine	2 mg in 1. inoc. 1 com { 2.	38 2 13 -	21 3 9 -	11 1 5 -	11 1 5 -	12 2 3 -	3 1 1 -	3 1 1 -	3 1 1 -	3 1 1 -
	3 mg in 1. 1 com { 2.	63 5 24 -	86 20 69 9	- -	- -	- -	- -	- -	- -	- -
	6 mg in 1. 1 com { 2.	45 5 15 5	20 5 10 -	12 - - -	12 - - -	3 - - -	5 1 1 -	5 1 1 -	5 1 1 -	5 1 1 -
Typhus vaccine	mg in 1. 1 com { 2.	" "	25 3 6 -	70 3 45 5	5 1 1 18	28 1 --	1 1 8 -	3 1 8 -	3 1 6 -	18 6
Para-typhus A vaccine	same { 1. " { 2.	" "	40 15 30 10	80 20 70 7	15 35 25 50	2 3 3 3	7 2 2 2	30 15 15 25	60 25	
Para-typhus B vaccine	" { 1. " { 2.	" 2	14 4 18 3	50 6 59 9	1 3 3 27	31 - - -	8 4 4 30	48 30 31 38		

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Highest Inoculation Fever

36.1-37.0 37.1-37.5 37.6-38.0 38.1-39.0 39.1-40.0

Inoculation	%	%	%	%	%
Mixed vaccine	2 mg in 1. inoc 1ccm	\$1.94	35.48	14.52	8.065 0
	2. " "	33.96	33.63	18.87	3.77 0
	3 mg in 1. 1ccm	0.90	43.00	29.50	15.90 2.27
	2. "	3.03	24.24	21.21	24.24 0
	6 mg in 1. 1ccm	0	30.00	40.00	25.00 5.00
Typhus vaccine	2 mg in 1. 1ccm	20.00	40.00	15.00	25.00 0
	2. "				
Paratyphus A vaccine	1 mg in 1. 1ccm	2.33	34.81	39.50	20.48 3.88
	2. "	5.59	38.47	40.31	14.04 1.59
Paratyphus B vaccine	1 mg in 1. 1ccm	8.40	35.19	37.20	16.50 2.69
	2. "	14.18	35.47	31.42	15.20 3.72
Paratyphus B vaccine	1 mg in 1. 1ccm	25.00	26.01	21.56	25.44 1.99
	2. "	13.63	31.55	31.08	22.23 1.51

From these tables one sees that the reaction to the inoculum with mixed vaccine is not much more violent than that of simple vaccine.

The agglutination titer of the serum after the immunization fluctuates between weak and moderately high but it should be pointed out that as Kolle, Kutscher, Hetsch and others maintain that the agglutination titer does not always run parallel to the protective power. Pfeiffer and Marx have made known that the blood serum with the karbolisiertem inoculum vaccine with bacillus do not agglutinate at all, aside from a single case in which agglutination titer amounted to 1:10, but the protective resistance 1:100-1:200. After my single experience the agglutination titer against typhus

and paratyphus B was frequently high, against paratyphus A however, it was very low.

I have sought to establish the protective resistance in animals. Mice were used as experimental animals. A definite amount of blood serum which had been drawn on the 10 th day after inoculum, a 3 fold lethal dose of culture was added and this injected intraperitoneally in the animal. For control, serum removed form the inoculum was used.

Table 13

Negative in 1:50	Agglutination titer					All together
	1:50	1:400	1:800	1:1600	1:3200	
Typhus	1 (8.3%)	1 (8.3%)	1 (8.3%)	5 (41.6%)	4 (33.3%)	12
Para-typhus A	10 (83.3%)	1 (8.3%)				12
Para-typhus B		2 (15.6%)	6 (50.0%)	3 (25.0%)	1 (8.35)	12

Protective power of blood serum afer inoculation witl the mixed vaccine  
Table 14

Sera						All together
	0.1	0.05	0.01	0.005	0.001	
Typhus	5 (25%)	10 (50%)	5 (25%)		10 (50%)	20
Paratyphus A		1 (5%)	2 (10%)	7 (35%)	10 (50%)	20
Paratyphus B			4 (20%)	5 (25%)	11 (55%)	20

This experiment was repeated in 20 other cases. From the table it is evident that the agglutination and the protective vaccination of serums in inoculum are not parallel.

These figures show that the animal in the case of a 3 fold deadly dose of serum lived because of the inoculum.

The agglutination came in the cases of typhus as the strongest in appearance while the protective work in paratyphus A and B was much greater than in typhus.

These experiments show that in the inoculum with mixed vaccine the protective power against typhus and paratyphus A and B can be obtained simultaneously in the human body.

#### Summary

④ The inoculum with the mixed vaccine of typhus, paratyphus A and B develops local and general reactions, but which are not as violent as in the inoculum with simple vaccine (amount of bacillus 1/8 of mixed vaccine).

⑤ Not only humans but also in animals which have been inoculated with mixed vaccine, it could be established that inoculum with mixed vaccine not only could lend protective power against typhus but also against paratyphus A and B.

Concluding I wish to express to His Excellency General Surgeon Dr. Kimura, Chief of Medical Bureaus of the Navy Ministry, my appreciation for his stimulation. In addition I wish to thank Dr. Shirano, General surgeon. Dr. Kato, head staff doctor, and Dr. Orimo, staff doctor, for all their kind help in the composition of this work.